## Remarks

Prior to this Amendment, claims 1-5 and 8-44 were pending. By this Amendment, claims 8-44 have been canceled without prejudice solely in response to the Restriction Requirement. The Applicant reserves the right to prosecute these claims in divisional applications. The Applicant confirms that claim 6 was intended to be canceled in the last response. Claim 2 has been canceled herein. New claims 45-48 have been added. Therefore, following entry of this Amendment, claims 1, 3-5, and 45-48 will be pending.

Claim 1 has been amended to recite that the EGFR/HER1 antagonist is an antibody. Accordingly, claim 2 has been canceled. Claim 3 has been amended so as to depend from claim 1 rather than canceled claim 2.

Support for new claims 45-48 is found in the specification as follows:

45 - page 17, lines 26-27

46 - page 13, lines 6-7

47 - page 11

48 – page 10, lines 10-19

**The rejections under 35 U.S.C. §103(a)**

Claims 1-3 and 5 were rejected as being obvious over U.S. Patent No. 6,129,915 (Wels); or U.S. Patent No. 4,943,533 (Mendelsohn); in view of Varani et al., 1998, Pathobiology 66:253-259 (Varani); and further in view of U.S. Patent No. 6,004,967 (McMahon).

Claim 2 has been canceled.

The cited references do not make obvious claims 1, 3, and 5 because they do not provide a reasonable expectation of success for the practice of the claimed methods of treating psoriasis. To appreciate why this is so, it is important to understand certain characteristics of psoriasis. Psoriasis is a disease (1) occurring in a particular location, and (2) arising as a result of defects in many types of cells. These characteristics are discussed more fully below.

(1) Psoriasis is a disease that encompasses a multitude of abnormalities in the epidermal and dermal layers of the skin. See Ben-Bassat & Klein, 2000, Curr. Pharm. Design 6:933-942 (Ben-Bassat),[1] p. 933, left column: "Psoriasis is an inherited spectrum of skin diseases characterized by epidermal hyperproliferation, disturbed differentiation, inflammation and excessive dermal angiogenesis." [citations omitted] See also Varani, p. 254, left column: "Psoriasis is a common inflammatory skin disease characterized by excessive epithelial cell proliferation, leading to epidermal thickening and expansion of epidermal rete pegs into the papillary dermal space."

(2) Although manifesting itself in the skin, psoriasis is a disease in which defects in a great number of different types of cells, many of which are not primarily found in the skin, are likely to play a role. See Ben-Bassat, p. 933, right column: "One hypothesis suggests that T-cell activation and increased sensitivity of psoriatic keratinocytes to T-cell derived cytokines participate in the pathogenesis of the disease. In addition, there are various interactions between keratinocytes, dendritic cells, immune/inflammatory cells and extracellular-systemic mediators from other organs of the body." [citations omitted]

The location of the disease and the types of cells involved must be kept in mind when evaluating whether a disclosure provides a reasonable expectation of success for methods of treating psoriasis.

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[1] This publication was cited in the Office Action dated October 29, 2002.

The two primary references cited, Wels and Mendelsohn, at most suggest the use of antibodies and antibody fragments to the epidermal growth factor receptor (EGFR) to treat cancers, *i.e.*, diseases having very different characteristics from psoriasis. The very different characteristics of psoriasis, as compared to the diseases treated in Wels and Mendelsohn, lead to a conclusion that the treatments of Wels and Mendelsohn do not provide a reasonable expectation of success for the present invention.

One reason for this conclusion is the uncertainty associated with antibody therapeutic agents *in vivo* reaching the proper target site in psoriasis and having a sufficient therapeutic effect on the proper cells when administered systemically, as required by the present claims. As is well-known in the art, the success of antibody therapy requires that the administered antibodies or antibody fragments reach the diseased target cells in amounts sufficient to have a therapeutic effect. There is nothing in Wels or Mendelsohn that would lead one of ordinary skill in the art to believe that antibodies to the EGFR can do this in the case of psoriasis.

Wels suffers from the following defects that prevent Wels from providing a reasonable expectation of success for the present invention:

- Wels is concerned solely with the treatment of cancer, not psoriasis,
- Wels contains no *in vivo* data, and
- Wels discloses the use of an antibody on types of cells that are not the same types as the cells involved in psoriasis.

Wels discloses that antibody fragments that recognize the EGFR can be cytotoxic *in vitro*, *i.e.*, in tissue culture, to certain types of cells. See, *e.g.*, Figure 3, which shows the cytotoxic effects of certain EGFR antibody fragments combined with toxins on A431 human squamous cell carcinoma cells. See also Figure 4, which shows cytotoxic effects on A431 cells and two types of breast cancer cells.

There are no data in Wels that would lead one of ordinary skill in the art to expect that Wels's antibody fragments, if administered systemically to a mammal (i.e., *in vivo*), would be able to localize to the skin in sufficient amounts to have a therapeutic effect on the cells of the skin that are involved in psoriasis and at the same time have a therapeutic effect on the non-skin cells involved in psoriasis so as to satisfy the present claims' limitation of being "effective to treat psoriasis." The types of experiments conducted by Wels (*in vitro* studies in tissue culture) and the cell types used (squamous cell cancer and breast cancer cells) differ so greatly from the claimed method of administration (systemically) and from the types of cells involved in psoriasis, that Wels cannot be said to provide a reasonable expectation of success for the claimed methods.

Mendelsohn does not provide a reasonable expectation of success either since Mendelsohn, like Wels, makes no mention of psoriasis.

Varani cannot provide the reasonable expectation of success lacking in Wels and Mendelsohn because Varani is directed exclusively to experiments carried out *in vitro*, in an organ culture system. Varani discloses no *in vivo* results. The authors of Varani do not state that their results provide a reasonable basis to begin treating psoriasis patients with antibodies. The authors state only that their results "may provide a useful tool" for studying psoriasis. See p. 253, last two sentences of the abstract:

> These data suggest that growth factors which act through the EGF receptor help to maintain the psoriatic phenotype in organ culture. They also suggest that organ culture may provide a useful tool with which to elucidate the pathophysiological mechanisms of altered keratinocyte proliferation and differentiation in psoriasis.

Varani administered antibodies for the purpose of studying psoriatic cells in organ culture. There is no hint in Varani that the authors considered their antibodies to be suitable for therapeutic use. It seems likely that if the authors of Varani thought their results provided a reasonable expectation of success for the treatment of psoriasis *in vivo* with antibodies, they would have said so. But they did not. In fact, they stated more-or-less the opposite. They

expressed doubt about whether their findings can be extrapolated to the *in vivo* situation. See p. 258, left column, 3rd paragraph: "Of course, it is difficult to extrapolate from *in vitro* findings to what might be occurring *in vivo*." This difficulty is compounded because growth factor receptors other than EGF-R may have a role in psoriasis. See Varani, page 258, left column, 3rd paragraph: "These results do not, however, exclude the participation of other growth factor receptors, such as members of the Erb B family." Varani's sentiments about the difficulty of extrapolating *in vitro* results to the *in vivo* situation are echoed by Ben-Bassat, at p. 936, left column: "*In vitro* studies have revealed various mechanisms, whose relevance to the *in vivo* situation is still not completely understood."

Varani cannot overcome the defects in Wels and Mendelsohn relating to the lack of predictability with respect to *in vivo* use of monoclonal antibodies in psoriasis because the problem of an antibody reaching its target cells simply did not arise in the experiments of Varani. In the organ cultures of Varani, antibody was directly applied to the psoriatic cells, and fresh amounts of antibody were easily delivered, ensuring that adequate levels of antibody were present. See p. 257, paragraph bridging left and right columns.

In view of the above considerations, Varani cannot supply what is lacking in Wels and Mendelsohn.

McMahon was cited for the proposition that "even in non-antibody arts, systemic administration of a therapeutic agent, intended to treat psoriasis by inhibiting EGFR activity, is known and envisioned." (Office Action, page 4, lines 4-6). McMahon cannot provide the reasonable expectation of success for the claimed invention that is lacking in Wels, Mendelsohn, and Varani because that lack of reasonable expectation of success hinges on factors peculiar to antibodies, *viz.*, the uncertainties associated with antibody therapeutic agents reaching the proper target cells in psoriasis and having a sufficient therapeutic effect on those cells. As recognized by the Examiner, McMahon is concerned with "non-antibody arts." McMahon does not disclose the use of antibodies to treat psoriasis. McMahon

discloses the use of quinazolines. Quinazolines, as is well known in the art, and as can be seen from the chemical structure disclosed in col. 2, ll. 35-45 of McMahon, are simple, low molecular weight, organic compounds. As is well known in the art, antibodies (and even their functional fragments) are complicated, large, protein molecules, usually containing multiple polypeptide chains. The pharmacokinetics (*i.e.*, the absorption, distribution, metabolism, and excretion) of antibodies are very different from the pharmacokinetics of simple, low molecular weight, organic compounds such as quinazolines. One cannot extrapolate from the use of simple substances such as those disclosed in McMahon to the use of antibodies to treat psoriasis. Success in the former does not predict success in the latter.

From the above discussion it should be concluded that Wels, Mendelsohn, Varani, and McMahon, neither separately or in any combination, provide a reasonable expectation of success for the practice of the claimed invention. Accordingly, it is respectfully requested that this obviousness rejection be withdrawn.

Claims 1-3 and 4 were rejected as being obvious over U.S. Patent No. 6,129,915 (Wels); or U.S. Patent No. 4,943,533 (Mendelsohn); in view of Varani et al., 1998, Pathobiology 66:253-259 (Varani); and further in view of WO 96/40210 (Goldstein).

Claim 2 has been canceled.

The cited references do not make obvious claims 1, 3, and 4 because, as discussed above, Wels, Mendelsohn, and Varani do not provide a reasonable expectation of success for the practice of the claimed invention and Goldstein cannot supply what is lacking in Wels, Mendelsohn, and Varani since Goldstein only pertains to potential treatments for cancer, and makes no mention of psoriasis.

In view of these considerations, the combination of Wels, Mendelsohn, Varani, and Goldstein does not make obvious the present claims.

In view of the above, it is respectfully requested that this obviousness rejection be withdrawn.

**New claims 45-48**

New claims 45-48 depend, either directly or indirectly, from claim 1. New claims 45-48 add limitations to claim 1 that do not affect the arguments above that demonstrate that the cited references do not make obvious claim 1. Therefore, the cited references do not make obvious new claims 45-48, either.

The time for responding to the Office Action was set for February 18, 2004. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: MAY 18, 2004

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